

Serial No. 09/676,053
Reply of May 14, 2007

REMARKS

Applicants are in receipt of the Examiner's Final Office Action mailed January 3, 2007. This Reply is being filed with a Request for Continued Prosecution, and should accordingly be consider a submission under 37 CFR 1.114(c) in accordance therewith.

Revocation and Substitution of Power of Attorney

With this Reply, Applicants have filed a Revocation and Substitution of Power of Attorney; this document includes the designation of the address associated with Customer Number 33197 as a new Correspondence Address.

Objections

Oath Or Declaration

The Examiner has objected to the Declaration as being defective due to the presence of non-initialed and/or non-dated alternations made therein. Accordingly, Applicants hereby submit a new Declaration of Inventors in compliance with 37 CFR 1.67(a), which identifies the present patent application by Serial Number and filing date. This objection is thus now believed to be moot.

Claim Amendments

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Independent claims 31 and 38 have been amended to replace the term "drug or other bioactive agent" with the term "neuropharmacologic agent", which appears in the specification at e.g., page 14, line 20. This amendment makes clear that the referenced agent has neuropharmacologic activity. As necessary dependent claims have also been amended to be consistent with this terminology.

Additionally, independent claims 31 and 38 have been amended to indicate that the active Clostridial neurotoxin possesses mouse lethality of 3.3×10^5 LD₅₀/mg or greater. Support for this amendment can be found e.g., at Table 2 on page 25 of the specification.

Claim Rejections

Applicants acknowledge the Examiner's indication that the rejection of claim 32 pursuant to 35 U.S.C. §112(2) and of claims 31 and 34-36 under the judicially created doctrine of obviousness-type double patenting have been withdrawn.

Applicants thank the Examiner for so indicating.

I. Rejection of claims 31-32 and 34-45 pursuant to 35 U.S.C. 102(b).

Claims 31-32 and 34-45 have been rejected as allegedly lacking novelty over Bizzini et al., U.S. Patent 4,594,336 for the reasons set forth in the Office Action mailed June 10,

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2005. Applicants respectfully traverse this rejection for the following reasons.

In order to anticipate a claimed invention each and every element of a challenged claim must be disclosed by a single prior art reference, and must be arranged as in the claim, in order for the prior art to anticipate the claim. *See Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 220 U.S.P.Q. 193, 198 (Fed. Cir. 1983). Moreover, "the reference must be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the art in the field of the invention." *In re Paulsen*, 30 F.3d 1475, 1478, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994).

The Bizzini reference has been described in prior Replies, which are hereby expressly incorporated by reference herein. In particular, the Bizzini reference is drawn to a thiolated polypeptide comprising a proteolytic fragment of tetanus toxin, called the B-IIb fragment, to which at least one sulfhydryl group is directly or indirectly bound. *See Bizzini, Abstract.* Bizzini states that medicines may be bound to this fragment, but such medicines "must have -NH₂ groups." *Id.* at column 6, lines 19-22.

Prior to thiolation the B-IIb fragment is "treated for [sic] eliminating the residual toxicity thereof." *Id.* at col. 4, lines 59-60 (emphasis added). The residual toxicity of the B-IIb fragment is removed by an immunoadsorption step, and the resulting eluted fragment is "not toxic in the mouse at a dose

of 1.9 mg." *Id.* at paragraph bridging columns 5 and 6(emphasis added). Finally, Bizzini informs that "in all the examples, there has been employed the B-IIb fragment as defined hereinbefore devoid of its residual toxicity"(emphasis added).

The present claims are directed to an active Clostridial neurotoxin joined to a neuropharmacologic agent, wherein the active neurotoxin possesses mouse lethality of 3.3×10^5 or greater and has bind specificity for a target never cell. No such composition is directly or indirectly disclosed by Bizzini, and thus the present claims are not anticipated by Bizzini.

II. Rejection of claims 31-32 and 34-45 pursuant to 35 U.S.C. 103(a).

Claims 31-32 and 34-45 are also alleged to be obvious over the disclosure of Bizzini. Applicants traverse this rejection for the following reasons.

As described above, Bizzini does not disclose compositions comprising an active Clostridial neurotoxin possessing mouse lethality of 3.3×10^5 or greater and a linked neuropharmacologic agent. Rather, Bizzini describes a tetanus toxin fragment prepared by freezing and thawing crude tetanus toxin and isolating a fraction thereof. This fragment is further purified by affinity chromatography expressly so that toxin activity may be "eliminated". Only after the toxin

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fragment is made "devoid" of toxic activity is it thiolated and conjugated to an amino group-containing medicine compound.

Thus, Bizzini discloses that his tetanus-based composition is "not toxic in the mouse", that toxic activity has been "eliminated", and that the fragment is "devoid" of toxic activity. Thus, Bizzini teaches away from the present invention, that is, directs the person of skill in the art to first remove the toxic activity from tetanus toxin before linking to a "medicine". Bizzini never uses an toxic neurotoxin to link to a therapeutic agent and indeed takes substantial efforts to remove this activity before it is used.

In contrast, the composition of the present invention possesses mouse lethality of 3.3×10^5 LD₅₀/mg or greater, and comprises an active Clostridial toxin.

For this reason Applicants submit that the rejection of claims 31-32 and 34-45 pursuant to 35 U.S.C. 102 and 103 over Bizzini is successfully traversed.

III. Rejection of claims 31-32, 35-41 and 44-45 pursuant to 35 U.S.C. 102(e).

Claims 31-32, 35-41 and 44-45 have been rejected as allegedly lacking novelty over Arnon, U.S. Patent No. 5,562,907 (the Arnon Patent). Applicants respectfully traverse this rejection for the following reasons.

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Under the relevant portion of Section 102(e), "a person shall be entitled to a patent unless . . . the invention (in this case, the invention of present claims 31-32, 35-41 and 44-45) was described in . . . 2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent. . . ."

As an initial matter, the Examiner has referred to the alleged applicability of "pre-AIPA" 35 USC §102(e) "when the reference is a U.S. Patent resulting directly or indirectly from an International application filed before November 29, 2000." Without affirming or denying the accuracy of this statement, Applicants believe that whether or not this is the case, it is not germane to the applied rejection of the present patent application.

Firstly, Applicants note that the present patent application is not a "reference"; rather in the present case, it is Arnon that is the reference being applied. Thus the changes to the AIPA referenced by the Examiner pertain to the applicability of the reference.

Secondly, regardless which version of 35 U.S.C. §102(e) is being applied, the result is the same, such Arnon does not claim priority to a foreign or international patent application.

Present 35 U.S.C. 102(e) states in full:

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§102 A person shall be entitled to a patent unless . . .
. (e) the invention was described in - (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language

Before the amendments made by the American Inventors Protection Act of 1999 and the Intellectual Property and High Technology Technical Amendments Act of 2002, the text of 35 U.S.C. §102 had not been amended since 1975, and Section 102(e) read as follows:

§102 A person shall be entitled to a patent unless . . .
. (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent

The present patent application is a divisional of U.S. Patent Application Serial No. 08/750,101, filed May 1, 1997,

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which was filed pursuant to 35 U.S.C. §371 from International Patent Application PCT/GB95/01253, filed May 31, 1995; this latter application in turn claimed priority to UK patent applications GB 9410871.9 and GB 10871.1, both filed May 31, 1994.

Under the relevant portion of 35 USC §104, an applicant for patent may establish a date of invention in a foreign country other than a NAFTA country as provided in 35 U.S.C. §§119 and 365. These sections state that a U.S. application may claim the benefit of the earlier filing date of an international patent application which claims priority in accordance the requirements of the PCT to the filing date of a prior foreign patent application.

Thus under either rule, the present patent application is entitled to its earliest priority date of May 31, 1994 to establish its date of invention.

Arnon Is Not Prior Art To The Present Application Pursuant To 35 U.S.C. §102(e)

The Arnon Patent was granted October 8, 1996 on U.S. Patent Application Serial No. 08/254,238, filed June 6, 1994. The '238 application was a continuation-in-part application of prior U.S. application Serial No. 08/062,110, filed May 14, 1993. Because §102(e) provides that an application is entitled to a patent unless the presently claimed invention was described in another's patent granted on an application

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filed before the [date of] invention by the applicant, the only way in which Arnon could be properly applied as prior art is if the exact invention now being claimed by the present application was described in Arnon's original 08/062,110 U.S. patent application, filed May 14, 1993. This is so, partially because Applicants' constructive reduction to practice occurred May 31, 1994, before the filing date of the Arnon CIP, filed June 6, 1994.

The case law abundantly supports this conclusion. Section 102(e) is a codification of Justice Holmes' opinion in *Alexander Milburn Co. v. Davis-Bournonville Co.*, 270 U.S. 390 (1926) (hereinafter *Milburn*), in which the United States Supreme Court held that a patent issued to the senior party after the filing date of the junior party's application (but filed before such date) may constitute prior art against the application, despite not having been used, sold, published or patented before the junior party's filing date because the senior party, having given a "complete and adequate description" of the junior party's invention upon filing his application, "had done all that he could to make his description public. He had taken steps that would make it public as soon as the Patent Office did its work. . . ." *Milburn*, 270 U.S. at 399 (emphasis added).

Application of 35 U.S.C. §102(e) or §§102(e)/103 to the Present Claims.

As always, in order to anticipate a claimed invention under 35 U.S.C. §102, a prior art reference must disclose each

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element of a challenged claim, the disclosed invention must be arranged as in the claim, and the disclosure must enable and adequately describe the invention sufficiently to have placed it in possession of a person of ordinary skill in the art. anticipate the claim. *See e.g., Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 220 U.S.P.Q. 193, 198 (Fed. Cir. 1983), *In re Paulsen*, 30 F.3d 1475, 1478, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994).

The Examiner has stated that Arnon discloses "recombinant toxins", and "optionally cation channel blocking agents", and has cited the Arnon Patent. Applicants do not agree in any event that the Arnon Patent describes the present invention. However, Applicants herewith file with the present RCE a Supplemental Information Disclosure Statement containing the abandoned Arnon parent application 08/062,110 having the May 14, 1994 filing date, demonstrating that this language was not disclosed by Arnon on such date.

The Arnon '110 application is drawn solely to methods involving the administration of a toxin, such a botulinum or tetanus toxin, followed by the administration of an "antitoxin" antibody preparation. There is absolutely no disclosure of a composition comprising a Clostridial toxin and an antibody, a drug, a medicine or a conjugated molecule. There is no discussion of recombinant toxins. There is no discussion of the subunits, such as the heavy or light chains of a Clostridial toxin.

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The applicability of 35 USC §102(e) (and of 102(e)/103 obviousness) where the alleged prior art is a continuation-in-part application adding new matter to an originally filed patent application was addressed by Judge Giles Rich, one of the two drafters of the 35 U.S.C. §102(e) in *In re Wertheim and Mishkin*, 209 USPQ 554(CCPA 1981)(hereinafter *Wertheim*). Judge Rich, writing for a unanimous 4 judge panel of the Court of Customs and Patent Appeals, first noted that under 35 U.S.C. §102(e) “[a]n abandoned application by itself can never be a [prior art] reference.” *Wertheim*, 209 USPQ at 562. Indeed, in situations such as the present one, in which the earlier application’s disclosure differs from that of the later patent, *Wertheim* mandates that only if the earlier application (here, the ‘110 Arnon application) describes “the invention” being challenged is the later reference properly prior art to the challenged claims. *Wertheim*, 209 USPQ at 564. Otherwise, the issued patent is not prior art to the claims under 35 USC 102(e).

Wertheim involved 102(e)/103 obviousness, but its rationale is applied to any 102(e) rejection (i.e., either anticipation rejections or obviousness rejections under §§102(e)/103) involving continuation-in-part applications. In *Wertheim*, the senior party had filed a series of continuations-in-part claiming priority to a great-grandparent application. The USPTO had rejected the junior party’s application based upon a disclosure in this great-grandparent application, which was then combined with other, unrelated references to assert a claim of obviousness.

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The *Wertheim* court held that the disclosure of the great-grandparent application contained in the later published patent was not prior art to the claims at issue. Judge Rich stated to permit an earlier application that did not describe the invention to establish an earlier filing date "in a situation where there are continuation-in-part applications ignores the rationale behind the Supreme Court decisions in *Milburn* and *Hazeltine* [[*Hazeltine Research Inc. v. Brenner*, 382 U.S. 252, 147 USPQ 429 (1965)]] that 'but for' the delays in the Patent Office, the patent would have issued earlier and would have been prior art known to the public." *Id.* at 563.

The *Wertheim* court then held that "if a patent could not theoretically have issued the day the application was filed, it is not entitled to be used against another" *Id.* at 564 (emphasis in original). Therefore, "the determinative question is whether the invention" claimed in the senior party's publication "finds a supporting disclosure in compliance with §112, as required by §120 so as to entitle that invention" claimed in the later application the filing date of the earlier application. *Id.* (emphasis in original).

The first paragraph of 35 U.S.C §112 requires an adequate written description and best mode to be disclosed, as well as an adequate teaching of the manner of making and using the invention. "Without such support, the invention, and its accompanying disclosure, cannot be regarded as prior art as of that filing date". *Id.*

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Thus, Judge Rich concluded, "only an application disclosing the patentable invention before the addition of new matter, which disclosure is carried over into the patent can be relied on to give a reference disclosure the benefit of its filing date for the purpose of supporting a §102(e)/103 rejection." *Id.* at 564. *See also* MPEP §2136.03(IV), 2100-95 (Rev 5, Aug. 2006).

For this reason, Applicants respectfully submit that Arnon is not prior art to the present patent application under either anticipation or obviousness theories, since the '110 Arnon application, the only application from which the Arnon Patent claims priority to have a filing date prior to the present application, does not contain any disclosure describing, or providing a reason for the person of ordinary skill in the art to make, the presently claimed invention.

Accordingly, Applicants submit that the present claims are neither anticipated by nor obvious over either Bizzini or Arnon and are therefore allowable, and respectfully request that the Examiner issue a Notice to that effect.

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CONCLUSION

Applicants have filed a Petition for a Two Month Extension of time to respond to the present Office Action. Kindly use Deposit Account 01-0885 for the payment of the Petition Fee, or for any other any charge now due, or to credit any overpayment.

Respectfully submitted,



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